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PHOSPHENES PRODUCED BY ELECTRICAL STIMULATION OF HUMAN OCCIPITAL CORTEX, AND THEIR APPLICATION TO THE DEVELOPMENT OF A PROSTHESIS FOR THE BLIND

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SUMMARY

1. To explore the feasibility of a visual prosthesis for the blind, human visual cortex has been stimulated during a series of surgical procedures on conscious volunteers undergoing other occipital lobe surgery.

2. Area no. 17 seems the most effective locus for such stimulation, at least in sighted or recently hemianopic patients.

3. Changes in electrode size and configuration, or in stimulus parameters, have little effect on subjective sensation.

4. Thresholds do vary depending on parameters, but not electrode size, and these effects have been studied.

5. Painful effects are associated with stimulation of the dura, but not of the calcarine artery and associated vessels.

6. Stimulation of a single electrode usually produces one phosphene, whose size ranges from tiny punctate sensations like 'a star in the sky' up to a large coin at arm's length. Very large elongated phosphenes, like those seen by Brindley's second patient, have not been reported despite the number of patients, electrodes, and combinations of stimulus parameters tested. These large phosphenes may be an effect of prolonged blindness.

7. Stimulation substantially above threshold may produce a second conjugate phosphene, inverted about the horizontal meridian.

8. Stimulation of a single electrode may also produce multiple phosphenes with no differential threshold.

9. Chromatic effects and/or phosphene flicker may, or may not occur. This can vary from point to point on the same patient.

10. Phosphenes fade after 10–15 sec of continuous stimulation.

11. All phosphenes move proportionately with voluntary eye movements, within the accuracy of our mapping techniques.

12. Brightness modulation can easily be achieved by changing pulse amplitude.

13. The position of phosphenes in the visual field corresponds only roughly with expectations based on classical maps showing the projection of the visual field onto the cortex.

14. Patients can usually discriminate phosphenes produced by 1 mm^2 electrodes on 3 mm centres, although this seems to be close to the limit of resolution.

15. Patterns of up to four phosphenes produced by four electrodes have been recognized. However, a variety of complex interactions have been reported.

16. Multiple phosphenes are co-planar, although patients are unable to estimate their distance.

17. Phosphenes appear immediately when stimulation is begun, and disappear immediately upon cessation of stimulation.

18. Future work must concentrate on blind volunteers to explore possible differences in subjective sensation produced after prolonged blindness, and to explore more complex pattern presentation which requires substantial periods of time with any given patient.

INTRODUCTION

Electrical stimulation of human visual cortex has long been known to result in sensations of light (or 'phosphenes') as recently reviewed by Brindley (1973). Most blindness involves pathology restricted to the eyes and peripheral visual pathways, which would be bypassed by cortical stimulation, and the ability to perceive such cortical phosphenes is retained even after prolonged deprivation of sight.

A number of investigators have therefore suggested exploiting this phenomena to produce a functional visual prosthesis (Krieg, 1953; Shaw, 1955; Button & Putnam, 1962). If each electrode corresponds to a single 'phosphene', implantation of an array of electrodes might provide a basis for transmitting images similar to those displayed on scoreboards. A few dozen electrodes should be sufficient for presentation of simple patterns, and somewhat larger arrays for reading at useful speeds (Brindley, 1965*a*). However, it was not until the pioneering human experiments of Brindley & Lewin (1968) that the possibility of such devices became widely accepted and active efforts begun by our group, and by others (Sterling, 1971).

Phosphene effects have been reported to include 'clouds', 'pinwheels', and complex chromatic phenomena (Penfield & Jasper, 1954) as well as simple punctate sensations 'the size of a grain of sago at arm's length' (Brindley & Lewin, 1968). The need for precise reports on such subjective

sensations dictates a human observer. Animal experiments, including those with trained primates, may be suggestive but do not provide information which can be conclusively extrapolated to humans. Doty has pointed out (1971) that some of the most unusual and important observations reported by Brindley's first patient would have been virtually impossible to discover based on animal experimentation, and he goes on to volunteer personally as an experimental subject.

Before attempting to construct a permanent implant, we decided to conduct a series of acute experiments involving volunteers undergoing neurosurgical procedures for removal of tumours or other lesions. The added risks of conducting stimulation experiments on such patients are very small, and in some cases such stimulation procedures are carried out for the purpose of cortical localization before resection. A second advantage of acute experiments is the ease of employing discrete wires between stimulation equipment and the electrodes. Because of the risk of infection, percutaneous leads are less satisfactory for chronic implants. However,

TABLE 1. Clinical summary

Case no.	Age	Sex	Hemi-sphere	Lesion	Field deficit	Surgical procedure
1	57	M	R–L	Meningioma	Hemianopia	Resection
2	33	M	L	Arteriovenous malformation	Notch	Resection
3	20	M	L	Arteriovenous malformation	Notch	Resection
4	52	M	R–L	Metastatic tumour	Hemianopia	Lobectomy
6	31	M	R	Arteriovenous malformation	Notch	Resection
7	58	M	L–R	Glioblastoma	Hemianopia	Lobectomy
8	27	F	R	Astrocytoma	Small notch	Resection
11	22	M	L	Arteriovenous malformation	Hemianopia	Clip vessels
13	37	F	L	Tumour (histological diagnosis uncertain)	Hemianopia	Lobectomy
17	60	M	R	Metastatic tumour	Hemianopia	Lobectomy
20	71	F	L	Meningioma	Very small notch	Resection
22	28	F	R	Benign cyst	Hemianopia	Lobectomy
24	50	M	R	Metastatic tumour	Hemianopia	Lobectomy
25	51	M	L	Glioblastoma	Hemianopia	Lobectomy
35	55	F	L	Arteriovenous malformation	None? (confrontation only)	Clip vessels
36	62	M	R	Glioblastoma	Hemianopia	Resection

Data are based on sixteen experiments involving fifteen volunteers (case nos. 8 and 22 involve the same patient) selected from our series of thirty-eight experiments. Of the remaining twenty-two experiments, six involved other neuroprostheses and five others were abandoned because the patient was uncomfortable and general anaesthesia was necessary. Ten more were eliminated because the pathology of the area was great, and no useful sensation could be produced. One experiment involved participation in a stimulation session on Brindley's first patient.

many engineering compromises are necessary to design a completely implanted system, and there are difficulties in monitoring to be certain that the implanted portion is performing as desired. A third advantage is the ability to study a comparatively large patient population, minimizing the effects of individual variability which necessarily affect studies employing only one or two subjects.

The principal disadvantage of studying volunteers undergoing other surgery is the difficulty in conclusively extrapolating the results from sighted patients, or from those with short-term hemianopias, to blind subjects. Other disadvantages include technical difficulties in conducting psychophysical experiments under local anaethesia in the operating room, the limited amount of time available with any given subject, and the fact that the cortex of interest is frequently affected by pathological processes.

METHODS

Although access to the visual cortex can be gained during a wide variety of neurosurgical procedures, we felt justified in proceeding only in those cases where a craniotomy flap exposing the occipital lobe was part of the routine surgical procedure. Suitable patients are very rare, particularly since we required emotionally stable volunteers able to cooperate under local anaesthesia. Consequently, cooperative arrangements were made with a number of major neurosurgical services, and cases have now been done in conjunction with twenty-one institutions distributed throughout the United States and Canada.

Whenever a suitable subject was located, a fully equipped team was dispatched from the University of Utah. Logistical arrangements permitted the team to set up at the host institution within 24 hr after notification, to prevent delaying non-elective surgery. Informed consent was obtained from each patient and family in conformance with applicable standards of medical practice (Katz, 1972) including the Nuremberg Code and Declaration of Helsinki. Patients were briefed on the type of sensations which might be expected, particularly flicker, changes in phosphene position with eye movements, and other special considerations. The need for reliable reports was repeatedly emphasized, and checked during experiments by use of false stimulation warnings and stimulation without notice.

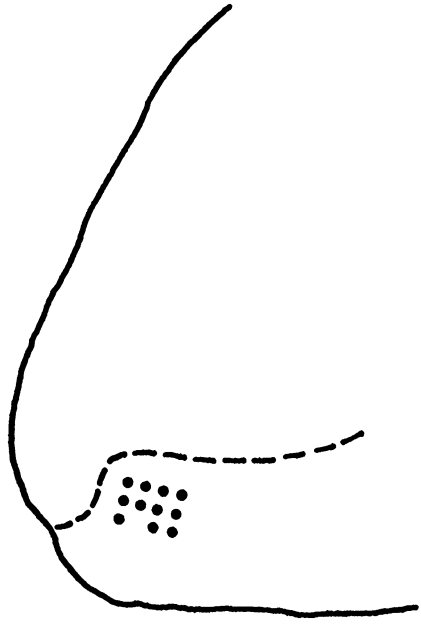
Pre-operative sedation was customarily accomplished with 10 mg I.V. Valium, with additional amounts during surgery as necessary. We suspect, but cannot prove, that Innovar® may interfere with production of cortical phosphenes based particularly on case no. 20. Most patients were also given prophylactic codeine for cough suppression.

Local anaesthesia was achieved with a variety of agents selected at the discretion of the individual surgeon. Our present choice is 1·0 % xylocaine extended with 0·1 % pontocaine, with or without additional epinephrine. It is extremely important to block the greater and lesser occipital nerves before infiltration of the scalp.

The craniotomy flaps were performed in conventional fashion,with and without use of head holders. However, use of power tools for opening the skull proved undesirable due to dural heating, noise and vibration which are uncomfortable for the patient. After the bone flap had been removed, pledgets soaked in xylocaine were found to be useful when placed along the outline of the dural flap. Great care was taken to be certain that no local anaesthetic contacted the brain.

Exposure of the cortex necessarily involves some thermal shock and mechanical trauma. To minimize such effects, experiments were conducted after the dura had been opened, but before any resection had been performed. We have been unsuccessful in producing phosphenes when stimulating after surgical resection. For example, in case no. 36 previously responsive areas were restimulated immediately after resection. No phosphenes could be produced, although the same areas were responsive again on the first post-operative day.

Stimulation equipment was usually positioned behind the surgeon, where it could be observed by everyone in the room, except the patient. This equipment consisted of two Grass S88 stimulators, equipped with modified PSIU-6A photo-isolation units to protect the patient in case of instrument failure.

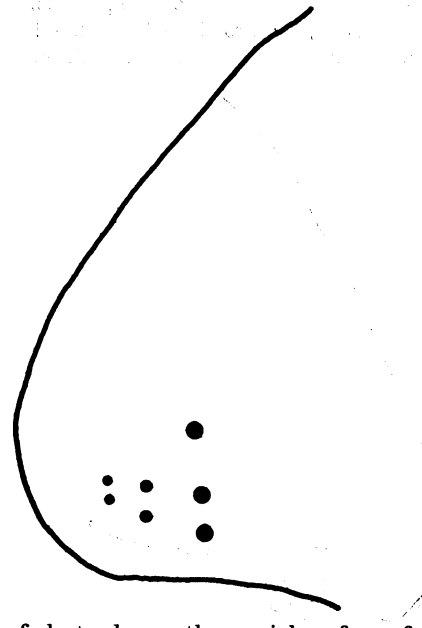


Text-fig. 1. Diagram of electrodes on the mesial surface of left occipital lobe in patient no. 25. Disks are 1 mm², on 3 mm centres. Number 1 is in the upper right, no. 3 is in the lower right, no. 10 in the upper left and no. 12 at the lower left. Electrode no. 9 had a broken wire, and is not shown in the drawing. The position of the calcarine fissure is estimated from study of the specimen removed after the lobectomy; however, landmarks were distorted by the tumour and surgical resection.

The voltage across the electrode was monitored using a Tektronix no. 2A63 differential amplifier and Tektronix no. 565 Oscilloscope. A second, identical differential amplifier was connected across a resistor in series with the electrode to monitor current. All stimulus parameters were set by oscilloscopic monitoring, rather than relying upon the stimulator calibration. An 8-channel (7 AM/FM plus audio edge track) Philips instrumentation tape recorder was used to simultaneously record stimulus parameters, and comments by the patient and experimental team.

Platinum iridium (90–10 %) ball electrodes mounted on a pencil-like holder were initially used, but proved unsuitable for stimulation of the mesial surface.

Consequently similar electrodes were attached to the flat surface of a standard brain retractor. However, electrode movement remained a problem, leading to development of ribbon cable electrodes consisting of pure platinum contacts and connecting wires, embedded in a Teflon matrix. These arrays can be easily inserted on the mesial surface, and will move with respiratory excursions of the brain. They can also be left in place after closure, permitting experiments for a few days until removed without re-opening the incision. Unless otherwise noted, the indifferent electrode consisted of a Bovie plate on the patient's lower back or buttocks.



Text-fig. 2. Diagram of electrodes on the mesial surface of the left occipital lobe in patient no. 25. Disks are 1 mm², 3 mm² and 9 mm² with the smallest, on 3 mm centres, nearest the tip of the pole. The calcarine fissure could not be identified in this patient, since vessels associated with the arteriovenous malformation restricted the amount of retraction possible.

The amount of time spent with patient no. 36 (about 45 min in the operating room, and 6 hr post-operatively spread over four sessions) was about equal to that available with all other patients combined. However, the majority of occipital lesions are so large before they are diagnosed that extensive resections or lobectomies are frequently performed and post-operative experiments are therefore impossible.

Case nos. 25, 35 and 36 confirmed earlier findings, using ribbon cable arrays which eliminated uncertainties resulting from movement of earlier, hand-held electrodes. The position of the electrode array in case no. 25 is shown in Text-fig. 1 and in case no. 35 is shown in Text-fig. 2.

After their first trial on case no. 25, these ribbon cable arrays were refined, and temporarily implanted through a Penrose drain in case no. 36. The drain and electrodes were removed on the 3rd post-operative day, after 1270 stimulations with no untoward results. A lateral skull film, taken before removal of the array, is shown in Plate 1.

RESULTS

These are organized according to the visual prosthesis design question that they help to answer. Virtually all previously published information on phosphenes which would be useful for design of a visual prosthesis is the work of Brindley and his associates. Consequently, our results will be compared with those reported by that group on their first (Brindley & Lewin, 1968; Brindley, 1970; Brindley, 1973) and second patient (Brindley, 1973; Donaldson, 1973; Brindley, Donaldson, Falconer & Rushton, 1972). This is facilitated by the generous opportunity that one of us (W.H.D.) was afforded to participate in a stimulation session involving their first patient.

1. *From what loci can phosphenes be produced?*

Our experience suggests that phosphenes suitable for use in a visual prosthesis can only be elicited from the primary visual cortex (also called area no. 17, striate, or OC). This differs from previous reports of phosphene production from association areas (Brindley *et al.* 1972; Brindley, 1972) and may be due to differences between blind subjects and those with short-term hemianopia. However, even if we are restricted to stimulating striate cortex exposed on the surface of the brain, there is sufficient surface area available to place a useful number of electrodes on 3 mm centres in virtually every patient (Stensaas, Eddington & Dobelle, 1974).

In case no. 1, phosphenes could only be elicited by stimulating the banks of the left calcarine fissure after removal of a meningioma of the falx. This tumour compressed the right lobe, from which no sensations could be produced. In case no. 2, the posterior edge of the craniotomy flap was about 1 cm lateral to the pole, and no sensations could be produced from the lateral surface although the lesion was circumscribed and the patient had only a small visual field deficit. During case no. 3 all aspects of the occipital lobe were explored along a series of radial lines emanating from the tip of the pole. Nineteen consecutive points thought to lie in association areas gave no result, until the electrode was moved to the bank of the calcarine fissure where repeated phosphene sensations could be elicited. In case no. 4, a total of 101 points were stimulated (some more than once) on the banks of both calcarine fissures. Seventy-six of seventy-eight stimulations on the left produced visual sensations, and eighteen of twenty-three on the right lobe, which was subsequently removed with the tumour, were responsive. Twenty points presumed to be on association cortex were explored in case no. 6, and only four of these produced visual sensation. By comparison, twenty out of twenty-six points presumed to be within the striate area produced phosphenes.

In case no. 7, twenty-seven points were stimulated on the mesial surface of the right occipital lobe through a small window in the falx after a left occipital lobectomy. Five of the eight points thought to lie on striate cortex were responsive, while only two of the nineteen thought to lie on association areas produced phosphenes. Subsequent cases (nos. 8–36) therefore concentrated on presumed striate cortex.

In all of these clinical impressions, localization was complicated by the extreme variability in the topographical distribution of striate cortex, and the distortions of surgical landmarks by space occupying lesions. The existence of a sharp demarcation line between responsive and non-responsive cortex is therefore best demonstrated from case no. 36, where

Text-fig. 3. Cortical positions resulting in phosphene production on case no. 36 are indicated by filled circles. Open circles indicate points from which no response could be obtained. The electrode was originally placed spanning the calcarine fissure, and the position of the fissure in this drawing is based on the phosphene map in Fig. no. 5. The interrupted lines suggest a demarcation between responsive and non-responsive cortex which is consistent with the limits of striate cortex.

this line could be consistent with the boundaries of striate cortex. In this patient, the electrode array (twelve 1 mm^2 disks on 3 mm centres) was placed across the calcarine fissure. As expected, this resulted in phosphenes distributed above and below the horizontal meridian, from all eleven functional electrodes (one had a broken wire and is not shown in the

drawing). The array was then partially withdrawn, so all electrodes rested above the fissure. Both positions of the array were verified radiologically. All points lying below the demarcation line in Text-fig. 3 were responsive, while no points lying above the demarcation line produced phosphenes.

We have also considered a variety of other sites for stimulation. Retina and optic nerve are degenerate in most blind people; the lateral geniculate body poses surgical problems and may also degenerate. Phosphenes are also produced (Marg & Dierssen, 1965) by stimulation of the geniculocalcarine tract. However, implanting arrays of electrodes in this tract is complicated by its variable location deep in the brain. We have made one unsuccessful attempt (case no. 9) to stimulate these fibres in the course of a shunt procedure on an adult hydrocephalic. Stimulation of the superior colliculus has been reported (Nashold, 1970) to produce phosphenes, but this locus has been rejected by us on the basis of small size and surgical inaccessability.

2. *What are the effects of changing electrode size or configuration?*

Our experiments suggest that electrode size has little effect on subjective sensation. Also, electrode size and hence current density does not seem to affect thresholds.

Initial experiments (case nos. 1–24) were conducted with platinum–iridium (90–10 %) ball electrodes varying in size from 0·5 to 2·0 mm in diameter. No difference in sensation was noticed as the application pressure (and hence the contact area) was changed, or when electrodes of different sizes were tested.

TABLE 2. Relationship between electrode area, wave form and threshold amplitude

	9·0 mm²			3·0 mm²		1·0 mm²	
Wave form	A4	B4	C4	B3	C3	A2	B2
+	2 mA	2 mA	—	2 mA	4 mA	1 mA	4 mA
+/−	2 mA	2 mA	3 mA	2 mA	—	2 mA	—

All stimuli 50 Hz, through a 1·0 μF series capacitor, with a 1·0 sec train duration. Pulse durations were 0·5 msec for each phase (1·0 msec total for biphasic stimuli). Time limitations prevented obtaining thresholds for electrode C4 with monophasic (+) stimulation, and for electrodes C-3 and B-2 with biphasic (+/−) wave forms. Electrodes A-3 and C-2 had broken wires.

In experiment no. 35, disk electrodes with surface areas of 1·0, 3·0 and 9·0 mm² were systematically compared. The protocol was primarily designed to investigate thresholds, and these were similar for all electrodes,

as seen in Table 2. There was no indication by the patient that the phosphenes produced by electrodes of different sizes were remarkably different. This constancy of subjective sensation and threshold, regardless of electrode size, is similar to earlier observations on somatosensory cortex (Libet, Alberts, Wright, Delattre, Levin & Feinstein, 1964).

Impedance of 1 mm^2 electrodes averages about 3 kΩ. This does not change dramatically with electrode size, although representation of this as a pure resistance is an oversimplification (Dobelle *et al.* 1973). Patients have reported no difference in subjective sensation when switching between an indifferent electrode on the buttock, and one attached to haemostats on bone at the edge of the craniotomy.

We have made very limited trials of bipolar stimulation between two identical electrodes on the surface of the cortex. In case no. 4 the patient reported a streaking sensation 'like my television going bad'. Patient no. 25 reported either one or two discrete phosphenes, depending on the electrode pair chosen for stimulation. More work will be required in this area.

Experiments on animal motor cortex (Asanuma & Sakata, 1967) suggest that intracortical micro-electrodes might produce phosphenes by stimulating a discrete population of neurones with currents of only a few microamps. We have felt justified in trying such electrodes only on cortex which was going to be surgically removed. This has not been successful, probably due to pathological involvement of the cortex in question.

3. *What are the effects of changing stimulus parameters?*

We have explored a variety of stimulus parameters and found that changes have little, if any, effect on subjective sensation. However, thresholds do change, and these effects have been studied. There are so many combinations and permutations of stimulus parameters that it is prohibitively time consuming to explore them exhaustively. Consequently it is possible, although unlikely, that some untested combination of wave form, amplitude, frequency, pulse duration and train length will have unique effects on subjective sensation.

Wave form. Monophasic (+), monophasic (−), and biphasic (+/− and −/+) wave forms have been explored with, and without, capacitive coupling. Significant delays (100 μsec) in the rise-time of the stimulus pulse have also been investigated. Subjects have denied significant changes in subjective sensation when interchanging these wave forms. Consequently, the wave form used for stimulation in any future visual prosthesis will probably be chosen because of electrochemical considerations relating to chronic stimulation (Dobelle *et al.* 1973) and/or factors involving engineering design.

The design of both Brindley's implants (Brindley 1965*b*; Donaldson, 1973) restricts them to production of monophasic (−) stimulation. For some experiments they have attempted to produce cortex (+) stimuli by maintaining a constant d.c. level, then stimulating with 'off' pulses. Brindley reports (personal communication) that this made no difference in the patient's subjective sensation, and this was also true in electrodes where the coupling capacitors had failed so that the stimulus pulse was d.c. coupled.

Beginning with case no. 1, we have repeatedly reversed the polarity of monophasic trains with otherwise identical parameters. During such experiments, the patients report no significant differences in subjective sensation. Biphasic stimulation (−/+ and +/−) was first tried, with similar results on case no. 8.

In case no. 25, patient reported no difference between cortex (+) monophasic stimulation with, and without, capacitive coupling (50 Hz, 1 msec pulse duration, 3 sec train duration). In case no. 35, monophasic (+) and biphasic (−/+ and +/−) wave forms were all employed. Thresholds for mono- and biphasic (+/−) wave forms were similar, as seen in Table 2, and the patient reported no significant difference in sensation regardless of wave form.

Patient no. 36 was asked to compare sequentially monophasic (−), biphasic (−/+) and monophasic (+) stimulation, and similarly reported no difference. In all trials the amplitude was 5 mA (10 mA peak-to-peak for biphasic), the train duration was 1·0 sec and the pulse repetition rate 50 Hz. The total current delivered in all stimuli was kept constant by having a pulse duration of 0·5 msec for each phase of the biphasic pulse, and 1·0 msec for the monophasic pulse.

Amplitude. All experiments have been conducted with constant current circuitry. Thresholds range from 1 to 5 mA, depending upon other parameters and individual variability. A current of 3 mA is typical, which is very similar to the results published for Brindley's first patient although our electrodes are larger, and not encapsulated by a post-implantation membrane. Changes in pulse amplitude produce corresponding changes in phosphene brightness, which were also reported by Brindley's first patient.

Pulse duration. Changing the pulse duration between 0·25 and 2·0 msec has little effect of subjective sensation. When using pulse durations less than 100 msec, brightness modulation can be achieved through such changes. This confirms similar reports by Brindley's first patient. Unfortunately, at these short durations thresholds are frequently in excess of 20 mA, based on our experience with patient no. 25. Such high instantaneous currents may present problems for chronic stimulation as well as for design of future microcircuit implants. Table 3 is based on case

no. 36, and shows the threshold current at ten electrodes, for each of five pulse durations.

Pulse repetition rate. Changing repetition rate between 30 and 200/sec has little effect on the subjective sensation. However, our patients confirm the report by Brindley's first patient that flicker becomes more pronounced at frequencies less than 30/sec. It is not clear whether the speed of the flickering changes, or if it is the intensity of the phosphene which is changing, since reports by different patients conflict on this point. Table 4 is based on case no. 36 and shows the threshold current for eleven electrodes at each of four frequencies.

TABLE 3. Relationship between pulse duration and threshold amplitude

Pulse duration for each phase	Electrode									
	B4	C4	A3	B3	C3	A2	B2	C2	A1	C1
1·000	5 mA	4 mA	5 mA	3 mA	3 mA	3 mA	2 mA	2 mA	3 mA	3 mA
0·500	—	5 mA	5 mA	4 mA	4 mA	4 mA	3 mA	3 mA	4 mA	3 mA
0·250	—	—	—	—	—	—	5 mA	5 mA	—	5 mA
0·125	—	6 mA	—	—	—	—	8 mA	7 mA	—	6 mA
0·62	—	—	—	—	—	—	—	12 mA	—	—

All stimulations were symmetrical biphasic (−/+), and currents are given for zero-to-peak values (for peak-to-peak, multiply by 2). Pulse repetition rate was 50 Hz, with a 1 sec train duration and 1·0 μF series capacitor. Electrode B1 had a broken wire, and electrode A4 did not respond to any stimulation. Because of time limitation, currents higher than 5 mA were not tested at 0·250 msec, higher than 8 mA were not tested at 0·125 msec, nor higher than 12 mA at 0·062 msec.

TABLE 4. Relationship between frequency, and threshold amplitude

Pulse repetition rate	A4	B4	C4	A3	B3	C3	A2	B2	C2	A1	C1
200 Hz	5 mA	5	3	2	2	2	2	2	2	2	2
50 Hz	—	5	4	4	4	4	4	2	2	4	2
25 Hz	—	—	4	—	4	—	—	—	3	—	—
12 Hz	—	—	8	—	—	—	—	—	—	—	—

All stimulations were symmetrical biphasic (−/+), and currents are given for zero-to-peak values (for peak-to-peak, multiply by 2). Pulse duration was 0·5 msec/0·5 msec, with a 1·0 sec train duration and a 1·0 μF series capacitor. Electrode B1 had a broken connecting wire. Because of time limitations, currents higher than 5 mA were not tested at 25 Hz, currents higher than 8 mA were not tested at 12 Hz.

Train duration. With our range of parameters, a train of between five and fifteen pulses is required to produce subjective sensation. This is a complex function of both amplitude and frequency. We have been unsuccessful in repeating Brindley's report of phosphene production with a

single pulse, although we have not used as high amplitude pulses as this apparently requires (at least 5× threshold).

This is quite important, since the minimum train length automatically determines an upper limit for frame repetition rate, and hence information transfer, in any future prosthesis. If 0·25 sec trains are used, the frame can be changed four times a second if there is no persistence. At one letter/presentation one might therefore transmit between 40 and 50 words/min, providing the patient could recognize and remember each letter. Table 5 shows the threshold train duration, in seconds, for eleven electrodes at each of two amplitudes.

TABLE 5. Relationship between amplitude and threshold train duration

	A4	B4	C4	A3	B3	C3	A2	B2	C2	A1	C1
4 mA	—	—	0·125	0·5	0·25	0·5	0·25	0·25	0·125	0·5	0·25
8 mA	0·250	0·250	0·06	0·125	0·125	0·125	0·125	0·125	0·125	0·125	0·125

All stimulations were symmetrical biophasic (−/+), and currents are given for zero-to-peak values (for peak-to-peak, multiply by 2). Pulse duration was 0·5/0·5 msec, at 50 Hz and 1·0 μF series capacitor. Electrode B1 had a broken wire. Each electrode in this Table was also tested with 1·0 and 2·0 sec trains and it is interesting that neither A4 or B5 gave any response with these longer trains.

Preliminary trials on patient nos. 2, 6 and 13 suggested that increasing the frequency (and hence the number of pulses for any given train length) is more effective than increasing the amplitude. Contrary to these expectations, the one trial completed on patient no. 36 at 100 Hz recorded thresholds which were higher than those at 50 Hz. Unfortunately, at this point we had to terminate the experiment because the patient was very tired and restless, and this unexpected result may be an artifact due to patient inattention.

4. *What differences might be expected due to cortical changes associated with prolonged blindness?*

Physiological (Wiesel & Hubel, 1965) and anatomical (Valverde, 1968) changes in the cortex of blind animals are well established in the physiological literature, although such studies have concentrated on deprivation of sight at the time of birth. The possibility of producing cortical phosphenes in patients after prolonged loss of vision is well established, and has recently been reviewed (Brindley, 1973). However, there may well be differences in the effective parameters, and the details of the subjective sensations, between newly blind patients and those with long-term deficits. Indeed, Brindley and his associates (G. S. Brindley, personal communication; Donaldson, 1973) attribute the differences between the phosphenes reported

by their two patients to this factor. This view is supported by the similarities between our results and those reported for their first patient.

Most of our patients have had field defects caused by interruption of the optic radiations, but attempts to correlate the patient's subjective sensations with duration of the field deficit are usually not meaningful because of difficulty in estimating the time course of the deficit. There are, however, two cases where hemianopic field defects of longer than a few weeks duration can be reliably documented. In both cases the subjects reported small, well defined phosphenes.

The same patient was involved in case no. 8 and case no. 22. The optic radiations were sacrificed during the first procedure, producing a complete homonymous hemianopia. Upon re-operation 10 months later, she reported phosphenes similar to the punctate sensations produced during the first operation. Patient no. 11 indicated that, for at least 5 years, he had been aware of severely limited vision on his right side. During stimulation he reported small sensations of light, 'like a match-head' in his blind field.

5. *Are there any painful side effects of stimulation?*

Brindley's first patient reported two types of somatic sensation. The first was apparently due to stimulation of the scalp by the indifferent electrode, and the second was thought due to stimulation of meningeal pain fibres. Such discomfort might limit the applicability of a future visual prosthesis. Our results when stimulating single electrodes suggest that this will not be a serious problem, but more work needs to be done with multiple electrodes.

In case no. 36, the patient repeatedly denied that pain, or other somatic sensation of any kind, was associated with the stimulation. This was reiterated during the post-operative testing period, and is important since studies in the operating room may be affected by use of sedatives and local anaesthetic agents.

Patients have not reported 'deep pain' similar to that experienced by Brindley's first patient. Instead, they invariably refer pain to the forehead and the area around the orbits, as does Brindley's patient when this sensation is severe. This referral of pain is almost certainly due to the innervation of the dura by the ophthalmic division of the trigeminal nerve.

Current spread to the walls of major blood vessels has not produced discomfort, even in experiments where we deliberately stimulated the calcarine artery and its branches. Abrupt movements of the dura, and particularly the falx, can be quite painful for the patient. However, there usually is rapid accommodation, and we do not believe that a permanent implant will be painful due to mechanical stimulation of these structures.

6. *Are phosphene sizes and shapes suitable to permit them to be used for synthesis of more complex patterns?*

Virtually all of the phosphenes reported by our patients seem suitable for use in a visual prosthesis. No patient has reported large elongated phosphenes of the type described by Brindley's second subject.

Before surgery, patient no. 3 had read portions of the paper by Brindley & Lewin (1968) and felt the sensations which he observed were similar, if not identical, to those reported by that patient. Patient no. 6 reported phosphenes ranging from '...about 1 mm I would say...just one of them small dots like they use for testing (visual fields)' up to '...about the size of a quarter at arm's length'. This range has been repeated throughout our series, with the very small ones being most common.

In most cases, the patients reported the phosphenes to be round but patients have occasionally reported short lines similar to the 'match stick' described by Brindley's first subject. For example, at one point patient no. 25 reported phosphenes about 10 mm long at arm's length.

7. *Does stimulation of a single electrode produce more than one phosphene?*

Brindley's first patient described a number of circumstances in which stimulation of a single electrode produced multiple phosphenes in the visual field. Our patients have reported similar phenomena, which divide into two groups.

The first variety is a cluster of closely spaced phosphenes which generally appear within a few degrees of each other. Our results to date agree with Brindley's failure to find a differential threshold for such clusters, but our attempts never employed increments of less than 0·25 mA because of the time required to manually reset the stimulators.

A second type of multiple phosphene, previously reported by Brindley's first patient, involves only a single phosphene at low amplitudes while higher amplitudes produce a second conjugate phosphene inverted about the horizontal meridian. Five out of the twelve electrodes in patient no. 36 produced such phenomena, as shown in Fig. 3. A differential threshold was easily achieved for electrodes A4, B4, C3. Electrode C1 produced no phosphene at 2·0 mA, one phosphene at 2·25 mA, and two phosphenes for all amplitudes above 2·5 mA. For electrode C2 the second phosphene was not always present, and a stable differential threshold could not be achieved.

Preliminary experiments on case no. 35 suggest that biphasic wave forms may have a greater tendency to elicit multiple phosphenes from a single electrode than monophasic stimulation. However, this is uncertain because of other variables and will require additional investigation.

8. *Are there any chromatic effects?*

Brindley's first patient was emphatic about the lack of chromatic sensation. This has been confirmed by some of our patients, but not others. These differences may reflect cortical changes after deprivation of sight, or may simply be a matter of individual variability. No correlation has been observed between changes in stimulus parameters and changes in colour. Small, polychromatic pinwheels were first reported by patients nos. 3 and 8, and were described in detail by patient no. 36. They remain fixed in the visual field, but rotate upon themselves, with spokes of different colours.

These chromatic effects are vivid, and patients generally report coloured phosphenes as being red, blue or occasionally green. It is interesting to speculate that on the relationship between these colours and the fundamental mechanisms of colour perception. On a number of occasions, subjects have reported 'unreal' colours. This was first reported by patient no. 3, whose best description was a 'non-spectral brown' or 'a colour from another world'. Two other patients in our series (cases nos. 22 and 36) have made similar observations during post-operative debriefings.

9. *Can brightness modulation be achieved for individual phosphenes?*

Brightness modulation can be repeatedly achieved by changes in pulse amplitude, irrespective of the other parameters involved. Brightness modulation can also be achieved by changes in pulse duration; however, this is most effective using high amplitude pulses with durations less than 100 μsec.

The number of discernible levels of brightness seems limited only by the maximum amplitude stimulation permitted up to at least 5 times threshold. We have not succeeded in studying the relationships between amplitude and relative brightness because of time limitations, nor between amplitude and absolute brightness since our patients proved unable to reliably match phosphenes against external lights.

10. *Are phosphenes sufficiently stable and reproducible to permit use in a prosthesis?*

Flicker. Brindley's first patient reported that phosphenes flicker, and this was confirmed by our patients nos. 3 and 4. However, patient no. 6, who had been trained pre-operatively to match phosphene flicker with an 'artificial phosphene' that he could control, reported that the phosphenes 'were not flashing...but it was steady', or 'a steady light about there'. At still another point, frustrated by our repeated insistence that he try to

match the flicker speed, he replied, 'well, if it is flickering, it is going awfully goddamned fast!'

On other points which did flicker, he was unable to match the rates, and this difficulty is clear if one tries to match flicker between two non-synchronous lights. Consequently, matching attempts were abandoned, and he reported that '...it comes and goes about this fast (taps finger at about 2/sec)' and on another occasion he stated, 'like going about like that (once again tapping at about 2/sec)'. Similar inconsistencies involving flicker, or lack thereof, were reported by patients nos. 8, 13 and 17. Patient no. 25 reported flickering sensations during seventy-four of 588 stimulations. During the course of our experiments we have seen no correlation of flicker rate with pulse, respiration, or stimulus parameters, other than an increased prominence of flicker at stimulation frequencies less than about 30/sec. This agrees with reports by Brindley's first patient.

Accommodation effects. Our results differ sharply from the report by Brindley's first patient that phosphenes do not fade, even with trains as long as 1 min. We first explored thresholds for various stimulus parameters by dynamically changing the parameter under study, while delivering a continuous train. This proved impractical because of accommodation effects. Thresholds increase, and the phosphenes fade during continuous stimulation of more than 10–15 sec. However, turning the stimulator off for a few seconds, and then turning it back on, generally caused the phosphene to reappear at its original brightness.

For example, patient no. 36 was asked to explore the effects of eye movements during a 30 sec train; the phosphene disappeared after about 15 sec.

Eye movements. Virtually all the patients in our series have commented on movements of phosphenes with eye movements. This confirms the report by Brindley's first patient. This could present problems for a future prosthesis, particularly in blind patients with nystagmus. Consequently, one must consider implantation of a microcircuit television camera in the orbit, attached to the extraocular muscles. Patients nos. 25 and 36 would occasionally shift their fixation point while mapping phosphenes in their visual field. Within the accuracy of the patient's ability to point, such deviations in gaze produced proportional displacement of all phosphenes in the visual field.

Due to technical problems involved in working with craniotomy patients, we have not attempted experiments on vestibular reflex eye movements of the type discussed by Brindley & Lewin (1968). We repeatedly monitor the patient's fixation and have seen no evidence of 'driven eye phenomena', in which electrical stimulation of the cortex elicits involuntary eye movements. However, patients will frequently move their

eyes when a stimulation begins in an attempt to fixate on the phosphene. Since the phosphene moves, they may then 'chase' it across the visual field.

Latency and persistence. Phosphenes seem to appear immediately when stimulation is begun, and disappear immediately upon cessation of stimulation. However, precise estimates are complicated by the patient's motor response time. This lack of phosphene persistence differs from the reports by Brindley's first patient, although we rarely stimulate with currents of 2–3 times threshold.

Repeatability. Using ribbon cable electrodes, artifacts due to movement of hand-held electrodes have been largely eliminated. Restimulation of the same point usually results in the same sensation each time. By the third post-operative day, patient no. 36 could identify the electrode being stimulated by the shape, special chromatic characteristics, and visual field position of the resulting phosphene. For example, the phosphene produced by electrode C3 was repeatedly described by the patient as resembling a colour-coded multiconductor cable, which was cut off and being observed end-on. Throughout the experimental period, he would repeatedly identify this phosphene as the '...same old cable'. This is encouraging, but experience with longer term implants is needed to evaluate the stability of phosphenes over substantial periods of time.

11. *Are phosphenes co-planar?*

Both sighted and hemianopic patients have difficulty in estimating the apparent distance of phosphenes. In partially sighted subjects such phosphenes are reported to float in space, and this has been confirmed in patients nos. 3, 6 and 25. Whenever multiple phosphenes are presented, they appear to be co-planar. This is of crucial importance for a visual prosthesis, since creating a display with phosphenes located at different apparent distances from the observer would be most difficult.

12. *How does the electrode position on the brain relate to the position of phosphenes produced by that electrode in the visual field?*

The phosphene produced by any given electrode appears in the visual field at a position which corresponds roughly to expectations based on classical maps showing the projection of the visual field onto the cortical surface. However, precise mapping is quite difficult to accomplish in the operating room. Phosphenes move with eye position, and are frequently too close together to be resolved due to inaccuracies in pointing. This difficulty is compounded in hemianopic patients, since they have no visual feed-back. Consequently, details of the map must be explored by determining the relative position of each phosphene among its neighbours.

This can be quite time consuming and is not practical during an acute experiment. For a given interelectrode distance, phosphene spacing will vary depending on the portion of the cortex being stimulated. Phosphenes produced near the centre of the field are usually closer together than those at the periphery.

In patient no. 25, all phosphenes were reported to be in the upper right quadrant, with the array resting on the lower bank of the calcarine fissure within 1 cm of the tip of the pole. This electrode consisted of twelve disks, in a rectangular (4×3) array, on 3 mm centres. All phosphenes were mapped within 5° of the fixation point, but were too closely spaced to be resolved by pointing. There was not enough time to explore the relative position of phosphenes in detail, except to get a general impression that electrodes nearer the tip of the pole produced more central phosphenes. No mapping experiments were attempted on case no. 35.

The map obtained during post-operative experiments with patient no. 36 is shown in Fig. 4. It is quite irregular; electrodes which are close together on the surface may, or may not, give adjacent phosphenes. Within the accuracy of the patient's ability to point and describe interrelationships, the map remained unchanged over the $2\frac{1}{2}$ days of experimentation. The array was moved and restimulated once during removal, but we did not attempt to construct a second map because of the time required.

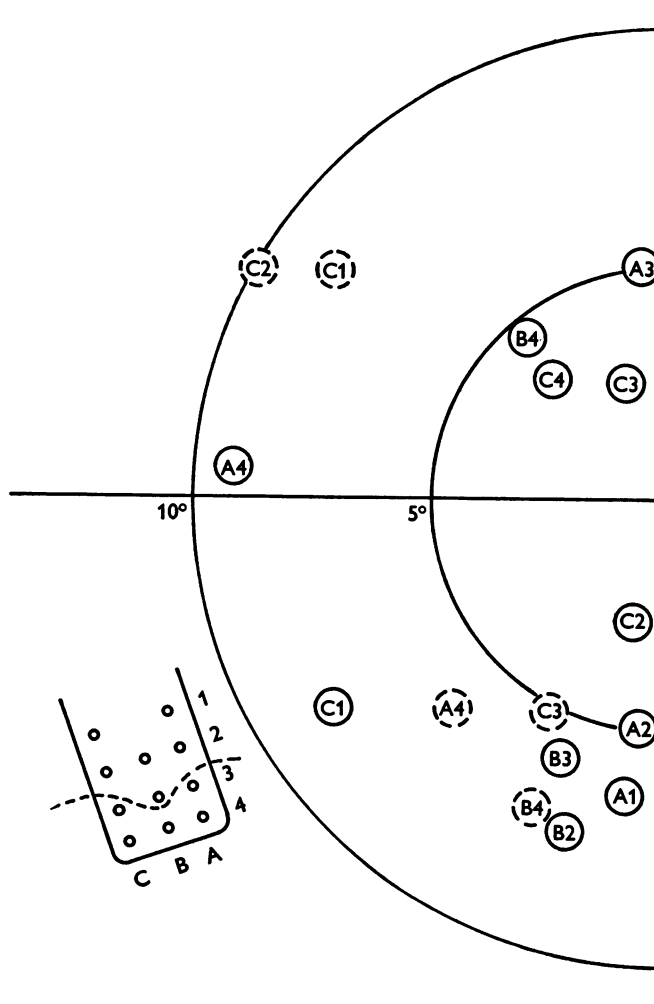
The electrode array spanned the calcarine fissure, and phosphenes clustered in two groups above and below the horizontal meridian. This is consistent with the expectation that the intervening portion of the field was mapped on cortex lying within the depths of the calcarine fissure. The position of the calcarine fissure is postulated based on whether adjacent electrodes produced phosphenes above or below the horizontal meridian. Unfortunately, the fissure could not be clearly visualized at surgery, and the electrode moved slightly during closing of the skull. Consequently, it was not possible to verify the position of the fissure on anatomical grounds.

13. *How closely spaced can electrodes be resolved, and what interactions are observed?*

We find that two-point discrimination breaks down between 2 and 3 mm, which is consistent with the reports of Brindley's first patient. A variety of interactions have been observed during simultaneous stimulation of multiple electrodes. Due to the complexity of the phenomena, and time limitations, these interactions have not yet been studied in detail.

Preliminary information was obtained in cases nos. 6, 8 and 13. It was further explored on patient no. 25, where a total of 104 presentations were made in which 2, 3 or 4 electrodes were stimulated simultaneously.

Our studies have concentrated on 1 mm² electrodes. Since electrode size seems to have little effect on phosphene size or thresholds it is unlikely that two-point resolution can be materially increased by using smaller electrodes. In fact, the requirements for chronic stimulation suggest the bigger the electrodes, the better. When we have varied the interlacing interval from 1 to 10 msec between pulses delivered to adjacent electrodes, it has not affected discrimination, confirming the report by Brindley's first patient.



Text-fig. 4. Phosphene map in the visual field for case no. 36. Phosphenes indicated by dashed circles appear only at high amplitudes. The electrode array and numbering system are also shown, along with a dashed line showing the postulated position of the calcarine fissure.

Recent anatomical studies (Stensaas *et al.* 1974) indicate that at least 359 mm^2 of striate cortex are exposed on the surface of any given hemisphere. Hexagonal packing on 3 mm centres permits about 15 electrodes/cm^2. Consequently, placement of between 50 and 200 electrodes per hemisphere should be possible even if we are restricted solely to striate cortex exposed on the surface of the brain. This should be more than sufficient for development of a useful prosthesis, particularly since both hemispheres are potentially available for placement of stimulating electrodes.

It may be possible to elicit phosphenes from areas nos. 18 and 19 in blind subjects (Brindley *et al.* 1972), or some yet untested combination of electrode configuration and stimulus parameters might increase resolution. The performance of any prosthesis should increase accordingly, barring interactions as larger arrays of electrodes are stimulated.

The most common interaction occurs when the space between the phosphenes fills in with light. For example, when patient no. 25 was asked to fixate and compare the position of phosphenes produced by sequential stimulation of electrodes nos. 2, 3 and 4 he reported, '...it moved over about a quarter of an inch...it moved over again about a quarter of an inch...it moved just a very faint hair'. When simultaneously stimulating electrodes nos. 1 and 2 he stated, 'Well, they're not very far apart because they kind of blend together. But you can tell one brightness from the other just slightly'.

Similar results were reported from electrodes nos. 2 and 5, 'Oh...I can't make out the difference between them. Looks like they have blended into one'. However, when testing electrodes nos. 5 and 8, the patient reported, 'Now I can see two (emphatic) and they're just about one half inch apart'.

A variant of this occurs when, upon stimulation of a second electrode, the two phosphenes begin to spin around each other in a localized area. This was first reported to us in case no. 8, but it is far less common. A third type of interaction occurs when delivery of subthreshold stimuli to neighbouring electrodes causes summation, and phosphenes expected from both electrodes are reported by the patient. This includes lowering the threshold for production of the high-amplitude 'double'.

Phosphenes produced by multiple electrodes are generally additive, but on some occasions expected phosphenes do not appear. We have succeeded in presenting a square with four electrodes. However, systematic study of pattern presentation will require substantial periods of time with a given patient. Such studies are crucial to the question of useful information transfer, and are best accomplished with a trained blind volunteer. For example, when simultaneously stimulating electrodes nos. 3, 4, 10 and 12, patient no. 25 reported, 'Oh yeah, I can see one, two...three...

I can't pick this other out down here, but its almost a square'. Restimulating the same pair he stated, 'I saw four, but two were bright, and two were dim'. Pointing to the tangent screen, he indicated a small square mapped within the central 5° of visual field. Such effects are complex, and their study requires more time than is available in the operating room.

DISCUSSION

Our results confirm most of the important observations which have been made by Brindley and his associates on their first patient (Brindley & Lewin, 1968). This includes unexpected findings such as a second 'high threshold' phosphene inverted about the horizontal meridian from single electrodes, and the movement of phosphenes with deviations in gaze.

Because of our flexibility in changing electrode configurations and stimulus parameters, we have also been able to expand these previously published observations. On a number of points, our findings differ sharply from those previously reported. This includes our observation that stimulation must be restricted to area no. 17, as well as differences on questions of chromatic effects and flicker. We believe that these differences can probably be attributed to changes occurring secondary to prolonged deprivation of sight, which supports the view of Brindley and his associates concerning the difference between their first and second patient.

We believe the point of rapidly diminishing returns has now been reached for acute experiments on volunteers who must undergo surgery for other reasons. Crucial problems at the moment include the need to explore differences in subjective sensation produced after prolonged blindness, and the need to explore more complex pattern presentation which requires substantial periods of time with any given patient. We believe these problems can be best investigated by temporary implantation of 'hard wired' electrode arrays in blind volunteers, after which a permanent prosthesis might be implanted as a second-stage procedure.

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EXPLANATION OF PLATE

Lateral skull film showing electrode array positioned on the mesial surface of the right occipital lobe in patient no. 36. Disks are 1 mm^2 on 3 mm centres, and the numbering is shown in Text-fig. 4. This film was taken after the array had been moved, as discussed in the caption to Text-fig. 3.